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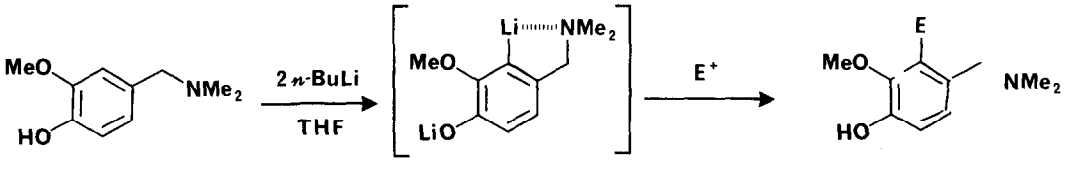
DIANION METALLATION REACTIONS OF N,N-DIMETHYLVANILLYLAMINE AND N,N-DIMETHYLISOVANILLYLAMINE

Dennis J. Hlasta* and Malcolm R. Bell
Sterling-Winthrop Research Institute
Rensselaer, New York 12144

The utility of dianion chemistry in the synthesis of polyfunctional aromatics is demonstrated by the direct lithiation of the vanillylamine 1 and by the metal-halogen exchange reaction of the bromo isovanillylamines 9 and 10.

Directed metallation reactions permit the selective functionalization of an aromatic ring ortho to a directing group and the preparation of contiguously polysubstituted aromatic compounds which normally are not readily available through electrophilic substitution reactions.[1,2,3] The utility of this reaction has been demonstrated by numerous applications to natural product synthesis.[4] This report describes the first example of a preparatively useful dianion (2) formed by direct lithiation of a phenolic substrate. The substitution requirements for the formation of the dianion 2 were examined thus demonstrating the types of stabilizing groups that are required for the formation of this type of a destabilized dianion. The importance of stabilizing groups for the formation of dilithiated aromatic ethers has recently been reported.[5] The usefulness of metal-halogen exchange reactions is demonstrated by the formation of the dianions 11 and 12 which were not available through direct metallation methods. Our findings in the dianion chemistry of vanillylamine 1 and of isovanillylamine 7 have provided us with a method for the preparation of the carbinols 3, 13 and 14 without the use of a phenolic protecting group.

In the course of our research it became necessary to prepare the amines 3, 13 and 14. Initially we planned to protect the hydroxyl groups in 1 prior to metallation but were unable to prepare a suitable derivative. The t-Bu and THP ethers could be prepared but only in low yield.



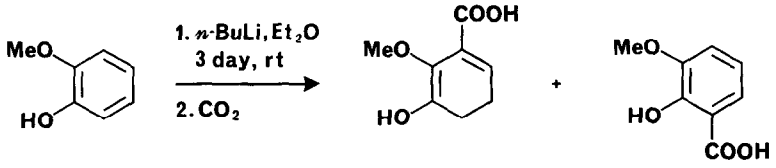
1 2 3

3a: E= $-C(OH)Ph_2$

3b: E= $-CH(OH)-C_6H_4-OCH_2Ph$

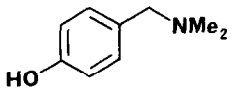
The allyl and benzyl ethers afforded mixtures when treated with n-butyllithium probably a result of deprotonation of the allyl or benzyl group.[6] The problem was solved by direct treatment of **1**[7] (0.2M) in tetrahydrofuran with 2. 2 equivalents of n-butyllithium. Quenching experiments with D_2O showed complete deuterium incorporation by NMR in the aromatic region after reaction for 3 hr at RT, providing evidence for the formation of the dianion **2**. Condensation of the dianion with benzophenone gave the triarylcarbinol **3a** in 65% yield.[8] The NMR spectra[8] of **3a** confirmed the site of lithiation as is shown in structure **2** since the aromatic protons displayed an ortho coupling constant of 8 Hz. The reaction is easily scaled up. On a 0.5 mole scale the dianion **2** was formed in 5 hr at room temperature, and addition of 4-benzyloxybenzaldehyde gave **3b** in 60% yield.[8]

Unprotected phenols have been ortho-metallated but the yields are too low to be preparatively useful.[9] For example, lithiation of o-methoxyphenol **4** gave very low yields of the isomeric benzoic acids **5a** and **5b**.[9a]



4 **5a** 2% **5b** 2%

To determine the requirements for dianion formation the phenols **4**, **6**,[7] and **7**[10] were treated with 2.2 equivalents of n-butyllithium in tetrahydrofuran (with and without tetramethylethylenediamine). Quenching experiments with D_2O showed no detectable dianion formation by NMR at room temperature for 1-2 days. In view of these failures it appears that in additon to the coordination group[3] ($-CH_2NMe_2$), the acid-base group[3] ($-OCH_3$) of the amine **1** is needed to increase the reactivity of the aromatic C-2 proton for lithiation and formation of the dianion **2**.



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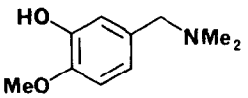

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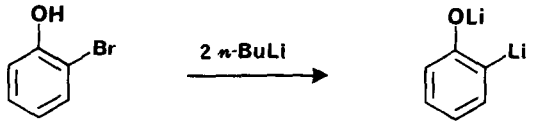
Functionalization of the isomeric phenol **7** has been accomplished via another route through the dianions **11** and **12**. The metal-halogen exchange reaction of o-bromophenol with n-butyllithium gives the dianion **8**.[11] Similarly the dianions **11** and **12** were prepared by metal-halogen

exchange of the bromophenols **9** and **10**[12] (0.1 M in tetrahydrofuran with 2.2 equiv. of n-butyllithium) and yielded the adducts **13** (40%) and **14** (49%), respectively.[8]



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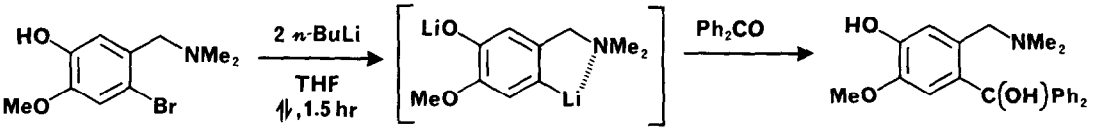
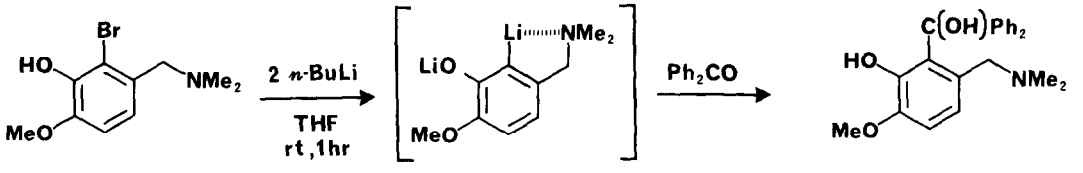


9 **11** **13**



10 **12** **14**

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7. Prepared by the reductive amination of the corresponding aldehyde (Me_2NH, MeOH, H_2(50 psi), Ra-Ni); vanillin, J.H. Short, D.A. Dunnigan, and C.W. Ours, Tetrahedron, **29**, 1931 (1973); 4-hydroxybenzaldehyde, E. Stedman, J. Chem. Soc., 1902 (1927).

8. Yields given were not optimized and are for isolated products having satisfactory NMR, IR, MS, and elemental composition. **3a**: Acetic acid salt, mp 173-179°C (dec.); IR(KBr) 1600 cm^{-1} (COO^-); MS m/e 363 (M^+); ^{1}H-NMR (pyridine-d_5) δ 2.00 (s,6H), 2.10 (s,3H), 3.10 (s,3H), 3.36 (s,2H), 6.90 (d,1H,J=8Hz), 7.12 (d,J=8Hz) and 7.23 (m) (8H), 7.70 (m,4H). **3b**: mp 168-170°C; MS m/e 393 (M^+); ^{1}H-NMR (pyridine-d5) δ 2.04 (s,6H), 2.56 (d,1H,J=12Hz), 3.46 (d,1H,J=12Hz), 3.98 (s,3H), 5.13 (s,2H), 6.81 (s) and 6.89 (d,J=8Hz) (2H), 7.0-7.7 (m,11H). **13**: mp 208-210°C (dec); MS m/e 363 (M^+); ^{1}H-NMR (DMSOd_6) δ 2.04 (s,6H), 2.81 (s,2H), 3.41 (s,3H), 6.14 (s,1H), 6.70 (s,1H), 7.3 (m,10H), 9.18 (bs,2H). **14**: Hydrochloride *monohydrate*, *mp* 175-181°C (dec); MS *m/e* 363 (M^+); ^{1}H-NMR ($CDCl_3$-DMSOd_6) δ 2.76 (s,6H), 3.75 (s,3H), 3.93 (s,2H), 6.64 and 6.87 (two overlapping d,2H,J=8Hz), 7.15 (m,10H).

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10. Prepared by the reductive amination of isovanillin (55%) (Me_2NH, MeOH, H_2(50 psi), Ra-Ni).

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12. **9** was prepared in 41% yield by bromination of **7**[10] (Br_2, HOAc, 48% HBr). **10** was prepared by bromination of isovanillin[13] (Br_2,HOAc) followed by reductive amination ($NaBH_3CN$, MeOH, Me_2NH).

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